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Clinical Study

Pre-existing structural abnormalities of the limbic system in transient global amnesia

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ABSTRACT

This study aimed to investigate the clinical and radiological findings in patients with transient global amnesia and to evaluate structural abnormalities using voxel-based morphometry. The subjects were diagnosed with transient global amnesia. For the voxel-based morphometry analyses, Statistical Parametric Mapping, running on the MATLAB platform (MathWorks, Natick, MA, USA), was employed to analyze the structural differences between patients with transient global amnesia and control subjects. Eighty patients met the inclusion criteria. Twenty-three patients (29%) were men, and 57 patients (71%) were women. There were significantly more women among the transient global amnesia patients compared with the general Korean population. MRI revealed hippocampal cavities in 41 patients (51%), and the incidence of such cavities was significantly different from that of the control subjects (24%). There were no differences in the clinical factors between the patients with and without hippocampal cavities. Diffusion-weighted imaging was performed in 54 patients, and 13 patients (24%) exhibited high signal intensity in the hippocampus. There were also no differences in the clinical factors between the patients with and without high signal intensities in the hippocampus on diffusion-weighted imaging. Twenty-six patients underwent three-dimensional volumetric T1-weighted imaging that produced results suitable for voxel-based morphometry, and these patients presented with gray matter volume reductions in the hippocampus, cingulum, and cerebellum. There were significant structural differences in the limbic structures between patients with transient global amnesia and the control subjects that might have contributed to vulnerability of the memory pathways of the patients with transient global amnesia.

1. Introduction

Transient global amnesia (TGA) is a disorder that is characterized by the sudden onset of transient memory impairment with anterograde and partial retrograde amnesia that lasts for several hours followed by complete resolution [1]. Data from clinical and psychometric studies have suggested explicit involvements of brain structures that are implicated in memory processing, such as the Papez circuit, in patients with TGA [2–4]. Altered perfusion or hypofunction of the temporal area has also been demonstrated in single-photon emission computed tomography (SPECT) and positron emission tomography studies [5,6]. Additionally, the published studies that have used the diffusion-weighted imaging (DWI) form of MRI have demonstrated that signal changes in the lateral hippocampus are present in patients with TGA [7,8]. Nevertheless, there is no direct evidence of structural abnormalities in areas implicated in memory processing in patients with TGA.

MRI-based measures of atrophy are regarded as valid markers of disease state and progression [9]. Voxel-based morphometry (VBM) was designed to increase the sensitivity of comparisons of the local compositions of different brain tissue types, while discounting positional and other large-scale volumetric differences in gross anatomy [10,11]. VBM is a fully automated, computerized, quantitative MRI analysis, therefore it is not biased toward any particular structure. However, limited studies have been conducted using VBM in patients with TGA.

This study aimed to investigate the clinical and radiological findings in patients with TGA, and to evaluate the structural abnormalities using VBM analysis.

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2. Materials and methods

2.1. Patient subjects

This study was conducted with the approval of the Institutional Review Board of Inje University. The study was performed using consecutive patients from a single, tertiary referral hospital. The subjects were diagnosed with TGA between March 2010 and December 2013. The inclusion criteria were patients diagnosed with TGA at Haeundae Paik Hospital, and patients with no structural brain lesions on MRI. The diagnoses of TGA were made according to the criteria of Hodges and Warlow [1]. The exclusion criteria were patients with a history of neurological or psychiatric disease due to the potential association with brain atrophy, or patients with a history of drug or alcohol abuse, because this might have interfered with cognitive performance. All patients underwent a standard neurological examination and a structured interview to obtain information on vascular risk factors (diabetes, hypertension and dyslipidemia) and characteristics of the episode (duration, precipitating event, and associated symptoms). The imaging evaluation involved DWI and three-dimensional (3D) volumetric T1-weighted images.

2.2. Control subjects

The control group consisted of 29 age and sex-matched healthy subjects. All subjects had a normal neurological examination and no exclusion factors in their medical history. All control subjects had normal MRI scans. Twelve subjects were men, and the mean age was 59.0 ± a standard deviation of 11.9 years.

2.3. MRI data acquisition

All scans were performed on a 3.0 Tesla MRI scanner (AchievaTx; Phillips Healthcare, Best, The Netherlands) equipped with an eight channel head coil. All subjects underwent conventional brain MRI protocols that included axial and coronal two-dimensional T2-weighted images, that were obtained with a turbo spin echo sequence (repetition time [TR]/echo time [TE] = 3000/80 ms, slice thickness = 5 mm, echo train length = 14, field of view [FOV] = 210 mm, and matrix size = 512 × 512) and axial and coronal two-dimensional T1-weighted images that were obtained with an inversion recovery sequence (inversion time [TI] = 800 ms, TR/TE = 2000/10 ms, slice thickness = 5 mm, echo train length = 7, FOV = 210 mm, and matrix size = 512 × 512). DWI was performed with a single-shot spin echo-based echo planer image with the following parameters: TR/TE = 6000/83.03 ms, slice thickness = 5 mm, echo train length = 53, FOV = 240 mm, matrix size = 256 × 256, and b-value = 2000 s/mm^2. The 3D T1-weighted images were obtained with a turbo field echo sequence with the following parameters: TI = 1300 ms, TR/TE = 8.6/3.96 ms, flip angle = 8°, and a 1 mm^3 isotropic voxel size. Sagittal-oriented high-resolution contiguous 3D T1-weighted images were obtained. To speed up data acquisition, sensitivity encoding parallel imaging with an acceleration factor of two was applied.

2.4. MRI data processing and VBM analysis

VBM, based on 3D T1-weighted images, was used to analyze volumetric differences. Image processing was performed using the VBM8 toolbox (Structural Brain Mapping Group, University of Jena, Thuringia, Germany), implemented in Statistical Parametric Mapping 8 (SPM 8, Wellcome Trust Centre for Neuroimaging, University College London, London, UK). The VBM data were processed in the standard manner including the following steps: spatial normalization to the Montreal Neurological Institute template, gray matter segmentation, intensity modulation using Jacobian determination, and spatial smoothing with 6 mm Gaussian kernel. For the group analysis, two sample *t*-tests, patients *versus* normal controls, were performed using a general linear model to identify whole brain gray matter alterations with significant differences. Significance was defined at the level of $p < 0.05$, after correcting for the false discovery rate to compensate for type 1 errors and applying an extent threshold of 400 voxels. To consider other effects such as age, sex, and total intracranial volume, the two sample *t*-tests were repeated once with these factors, which were entered as covariates.

2.5. Statistical analysis

We compared the clinical factors between the patients with and without signal changes in the hippocampus on DWI [12] and investigated the incidence of hippocampal cavities in patients with TGA [13]. The hippocampal cavities were detected based on the agreement of two investigators. Additionally, we compared the clinical factors between the patients with and without hippocampal cavities. These comparisons were made using chi-squared tests or Fisher's exact tests for categorical variables, and Student's *t*-tests or Mann–Whitney U tests for numerical variables. The categorical variables were presented as frequencies and percentages. The numerical variables with normal distribution were presented as the mean ± standard deviation, and those without normal distribution were described as the median with the 95% confidence interval (CI) and ranges.

3. Results

The numbers of patients who underwent structured interviews to obtain the clinical factors and who were subjected to radiological investigations are reported in Table 1.

3.1. Clinical factors

Eighty patients met the inclusion criteria. Twenty-three patients (29%) were men, and 57 patients (71%) were women. There were significantly more women among the TGA patients compared with the general Korean population ($p < 0.001$; 5,811,891 men [44%] and 7,397,720 women [56%] out of 12,209,611 Korean subjects between 50 and 79 years old based on the 2010 data from the Korean Statistical Information Service). The mean age of onset was 60.3 ± 7.3 years. Among the patients with TGA, the presenting TGA event was the first such event in 77 patients, and three patients reported previous episodes of TGA. The median duration of amnesia was 5 hours (95% CI 4.0–6.0 hours, range 0.5–23 hours). Thirty-five (44%) of the 80 patients had a history of vascular risk factors, with hypertension in 27, diabetes in 10, and dyslipidemia in eight patients. Forty-four patients (55%) had a history of precipitating events, with emotional stress in 26, physical effort in nine, and water contact/temperature change in nine patients. Eleven patients (14%) had associated symptoms, with headache in four, general weakness in three, nausea in three, and dizziness in one.

Table 1
Numbers of patients with transient global amnesia who underwent structured interviews to obtain clinical factors, radiological investigations, and electroencephalography

Medical examination	n
Structured interview	80 (100%)
Conventional MRI including T1 and T2-weighted imaging	80 (100%)
Diffusion-weighted imaging	54 (66%)
Three-dimensional volumetric T1-weighted imaging	26 (33%)